CLUSTER ANALYSIS OF DISORDERS CHARACTERISED BY IMPULSIVITY IN PATIENTS WITH METHAMPHETAMINE USE DISORDER

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DECLARATION

I know that plagiarism is wrong. Plagiarism is to use another's work and pretend that it is one's own.

I, Edrich Rall, hereby declare that the work on which this thesis is based is my own (original work) and that neither the whole work, or a part of it, has been submitted in fulfillment of another degree.

I have used the APA 6th edition convention for citation and referencing. Each contribution to, and quotation in, this project from the work(s) of other people has been attributed, and has been cited and referenced.

This thesis titled "Cluster analysis of disorders characterized by impulsivity in patients with methamphetamine use disorder" is my own work.

I have not allowed, and will not allow, anyone to copy my work with the intention of passing it off as his or her own work.

Signature 

Date: 20 December 2018

DEDICATION

I wish to dedicate this writing to my parents, Andre and Daphne Rall, who unconditionally invested in my tertiary education the past 10 years.

ACKNOWLEDGEMENTS

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ABSTRACT

Background

Individuals with methamphetamine use disorder (MUD) frequently present with psychiatric comorbidities with impulsive features. Little research has been conducted on comorbidity with impulsive features in MUD. Therefore, this cross-sectional study aimed to delineate comorbid disorders with impulsivity in adult patients with a primary diagnosis of MUD.

Methods

Participants with lifetime MUD were included. Well established measures screened for comorbid psychiatric disorders with impulsive features. Illness severity was measured by the Yale Brown Obsessive-Compulsive Scale – adapted for drug use. The UPPS-P Impulsive Behavior Scale was used to assess impulsivity levels. A cluster analysis (CA) of lifetime comorbid disorders with impulsive features was performed. Demographic and clinical correlates of each identified cluster were identified.

Results

Sixty five (n = 65) adults with a primary diagnosis of MUD took part in the study. They were predominantly female (44 females; 21 males), with ages ranging between 18 and 44 years (mean = 30 years; SD = 6.53). The CA rendered 4 groups. Cases (n=12) in the “alcohol cluster” presented with AUD as their only *impulsive* disorder other than MUD. Cases (n=19) in the “healthy cluster” had no comorbidity. Cases (n=15) in the “antisocial cluster” all had comorbid antisocial personality disorder as well as polysubstance use disorders. Cases (n=19) in the “borderline cluster” had borderline personality disorder and polysubstance use disorders. Illness severity (Y-BOCS-du: p=0.03) and impulsivity levels (UPPS-P: p=0.01) differed significantly between the clusters. The “alcohol cluster” had the highest illness severity and the “antisocial cluster reported the highest levels of impulsivity.

Conclusion

The findings of this contribute to the paucity data on impulsivity in MUD and may have implications for treatment. Understanding how these conditions cluster in MUD, and remaining cognizant of the demographic and clinical correlates of each cluster in MUD, could potentially enable clinicians to

identify patients who are at higher risk for engaging in risky behaviors rendering them more vulnerable to treatment non-adherence or relapse

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LIST OF ABBREVIATIONS

ADHD: Attention Deficit Hyperactivity Disorder

ASPD: Antisocial Personality Disorder

AUD: Alcohol Use Disorder

BD: Bipolar Disorder

BPD: Borderline Personality Disorder

CUD: Cannabis Use Disorder

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

ICD: Impulse Control Disorder

MA: Methamphetamine (“Tik”)

MINI: The Mini International Neuropsychiatric Interview

SU/UCT MRC: Stellenbosch University / University of Cape Town Medical Research Council Unit on Risk and Resilience in Mental Disorders

MUD: Methamphetamine Use Disorder

MxUD: Methaqualone (Mandrax) Use Disorder

SACENDU: South African Community Epidemiology Network on Drug Use

SCID-5-SUD: The Substance Use Disorder module of the Structured Clinical Interview for DSM-5 Disorders

SCID-II: The Structured Clinical Interview for the Diagnosis of Personality Disorders

SCID-OCSD: The Structured Clinical Interview for the Diagnosis Obsessive-Compulsive Spectrum Disorders

SU: Stellenbosch University

SUD: Substance Use Disorder

UCT: University of Cape Town

UPPS-P: The UPPS-P Impulsive Behavior Scale

Y-BOCS-du: The Yale-Brown Obsessive Compulsive Scale Modified to Reflect Obsessions and Compulsions Related to Drug Use

CHAPTER ONE

INTRODUCTION

Introduction

This chapter provides a literature review of current knowledge on methamphetamine use disorder (MUD) and psychiatric disorders characterised by impulsive features. In addition, the main focus of the research project is highlighted, including a rationale for the study, objectives and hypotheses, and a suggestion for a target journal for publication of this work.

Context

Methamphetamine (MA) use seems to be increasing globally (Akindipe, Wilson, & Stein, 2014). It has reached epidemic proportions in South Africa, particularly in the Western Cape Province (Dada et al., 2016; Dada, Burnhams, et al., 2017; Plüddemann et al., 2013) where early adulthood (Meade et al., 2012), low educational levels (Meade et al., 2012; Semple, Zians, Grant, & Patterson, 2005; Watt et al., 2014) and mixed ancestry (Akindipe et al., 2014; Chetty, 2015; Harker et al., 2008) have been identified as risk factors for MA use. A large majority of those who use MA develop methamphetamine use disorder (MUD).

Methamphetamine use disorder is a psychiatric condition, classified as one of the substance-related and other addictive disorders in the Diagnostic and Statistical Manual of Mental Disorders (fifth edition) (DSM-5) (American Psychological Association (APA), 2013). Typical of MUD is the repeated unsuccessful attempts to cut down or stop using the drug, and clinically significant distress and functional impairment in several domains of life (APA, 2013). For example, individuals with MUD often neglect major obligations such as work, studies, family and even recreational- and other important social activities (APA, 2013). In addition, in MUD there is often a disregard of negative consequences that may affect the user or others (Brewer & Potenza, 2008; Fineberg et al., 2014). Individuals with MUD often spend vast amounts of time to obtain, use or recover from the effects of MA – even in hazardous situations (APA, 2013). Additionally, MUD has been linked with problematic impulse control (Brooks et al., 2017; Terzi et al., 2017; Verdejo-García, Lawrence, & Clark, 2008). According to Mahoney et al. (2015) and Hoffman et al. (2006), patients with MUD score significantly higher in impulsivity assessments compared to healthy controls. In comparison to users of other stimulant use disorders (e.g. cocaine use disorder), patients with MUD also score higher on

impulsivity assessments (Winhusen et al., 2013). While methamphetamine and cocaine are both stimulants, they have some key differences that could lead to different impulsivity profiles in their users. One key difference entails the relative length of subjective effects, which is considerably shorter for cocaine (Winhusen et al., 2013). In addition, it has been shown that users of MA and users of cocaine are both impaired on cognitive measures (e.g., perceptual speed, manipulation of information, verbal recall) between methamphetamine- and cocaine users, but the type and degree of impairments are somewhat different (Winhusen et al., 2013; Sim et al., 2001). Many overlapping definitions of impulsivity exist. For example, impulsivity has been defined as a trait leading to behavioral actions which are poorly planned or conceived, prematurely expressed, unduly risky, or inappropriate to the situation, and undesirable consequences usually result (Robbins, Gillan, Smith, Wit, & Ersche, 2012; Semple, Zians, Grant, & Patterson, 2005). This is partly consistent with DSM-5 (APA, 2013) which describes impulsivity as the actions that occur in the spur of the moment, hastily, and without forethought. These impulsive actions, typically seen in MUD, have high potential for harm to oneself or to others. Sensitivity to reward anticipation, delay aversion and poor planning are also typical of impulse dyscontrol (Hamilton et al., 2015; Pattij & Vanderschuren, 2008; Robbins et al., 2012; Roháriková, 2016; Semple et al., 2005) and may be reflected in the desire for immediate rewards and without the ability to delay gratification; or in social intrusiveness, such as interrupting others excessively; or in making important decisions without considering the long-term consequences that may often turn out to be problematic (APA, 2013). Whereas some authors has suggested that impulsivity may be adaptive in some circumstances, it is generally regarded as a dysfunctional trait that can be associated with actions that are antisocial, destructive or harmful to self or others, and inappropriate to accepted social standards (Verdejo-García et al., 2008). It is a complex phenomenon, and as can be seen from the previous definitions, problematic for the individual on multiple levels. Impulsivity may increase the likelihood of using stimulant drugs which in turn may increase impulsivity, leading to potentially hazardous use - a vicious cycle indeed. In other words, individuals with impulsive features may be at higher risk to experiment with MA, and MA use in turn is associated with increased impairment of behavioral control or impulsivity. The role of impulsivity as a precursor to developing a SUD, and also as a consequence of chronic drug use, has become apparent in recent literature (e.g. Lanesman et al, 2019).

Various authors report psychiatric comorbidity in MUD (Morisano, Babor, & Robaina, 2014; Plüddemann et al., 2013; Warden et al., 2016). According to Akindipe et al. (2014) and Harker et al. (2008), psychiatric disorders may also be more prevalent in MA-using individuals compared to the general population. Mania and hypomania are frequently found among patients with MUD (Akindipe et al., 2014). Lin et al. (2004) found that comorbid polysubstance use and SUDs are prevalent in MA users and Salo et al. (2011) identified that almost 60% of patients with MUD have a comorbid SUD. Substance use disorders in MUD range from alcohol use disorder (AUD), other stimulant use disorders (such as cocaine), cannabis, and sedative hypnotics and anxiolytics (Salo et al., 2011) (such as methaqualone / mandrax). Lin et al. (2004) also found that "behavioral addictions" such as gambling disorder (GD) is sometimes seen in the MUD population. Furthermore it is well documented that personality disorders such as antisocial personality disorder (ASPD) and borderline personality disorder (BPD) frequently occur in MUD (Plüddemann et al., 2013). These disorders co-occurring with MUD may have strong links to impulsivity (Dawe, Gullo, & Loxton, 2004). In conclusion, MUD is a psychiatric condition associated with impulsive features, and often co-occurs with disorders also characterized by impulsivity.

Study Rationale

Little research has been conducted on MUD and psychiatric comorbidity with impulsive features. Also, the research that does exist has been in the context of drug use in developed countries, with few studies having been conducted in low resource settings like South Africa (SA) (Lanesman et al., 2019). This study responded to recent pleas that highlighted the need for further research on MA use in South Africa - as a matter of social development, safety and public health (Mushanyu, Nyabadza, & Stewart, 2015; Watt et al., 2014; Wyk & Stuart, 2011). According to the most recent report by the South African Community Epidemiology Network on Drug Use (SACENDU), the Western Cape Province where this study was conducted, has the highest prevalence of MUD of all provinces in South Africa (Dada, Erasmus, et al., 2017), making this an ideal location for this research endeavor.

Furthermore, it appears that few studies exist on impulsive comorbidity in this population (Glasner-Edwards et al., 2008; Shoptaw, Peck, Reback, & Rotheram-Fuller, 2003). Methamphetamine use disorder is associated with significant mental health problems (Akindipe et al., 2014; Weybright, Caldwell, Wegner, Smith, & Jacobs, 2016) and psychiatric comorbidities may

arguably be seen as a predisposition for, or a consequence of, continued drug use (Yen & Chong, 2006). Many psychiatric disorders are characterized by impulsivity and often feature in patients with MUD. .

Therefore the primary aim of the study was to delineate disorders characterized by impulsivity in a sample of adult patients with a primary diagnosis of MUD by means of a cluster analysis (Ward's method) (CA), and to explore the demographic and clinical correlates of each identified cluster. Cognizance of the theses correlates of impulsivity in MUD can enable clinicians to identify patients who are at high risk for engaging in risky behaviors such as sexual promiscuity, rendering them more vulnerable to treatment non-adherence or relapse, or other difficulties such as HIV or sexually transmitted infections (e.g. Winhusen et al., 2013). The investigation may thus potentially guide treatment, and ultimately improve outcome in these patients.

The identified objectives and hypotheses were as follow:

Objective 1: To use structured diagnostic interviews to determine psychiatric comorbidity in adults with MUD.

Hypothesis 1.1: Psychiatric comorbidity is common in adults with primary MUD.

Hypothesis 1.2: Psychiatric disorders characterized by impulsivity are common in adult MUD.

Objective 2: To delineate impulsive comorbid disorders in MUD using a cluster analysis (CA) method.

Hypothesis 2.1: Given the heterogeneous nature of impulsivity, comorbid disorders in MUD that are characterized by impulsivity will group into 2 or more clusters using a CA.

Objective 3: To explore the association of the identified clusters with demographic (age, gender) and clinical variables (i.e. illness severity, level of impulsivity).

Research Setting

Recruitment was done in the Western Cape Province of SA. Semi-structured interviews were conducted in a private office (by the incumbent, Mr Edrich Rall) - either at a treatment center,

rehabilitation organization, or at the Stellenbosch University (SU) / University of Cape Town (UCT) Medical Research Council's Unit on Risk and Resilience in Mental Disorders (SU/UCT MRC).

Ethical Considerations

The research proposal was submitted for ethical approval at the Human Research Ethics Committee (HREC) at UCT. Ethical approval for the study was received on 12 March 2018 (UCT HREC reference number: 074/2018) (Appendix 1).

Participants who provided signed consent were included in the study. Information on the study aims and procedures was available in Afrikaans and English. All participants participated voluntarily and were informed that they may refuse or stop participation at any time without negative consequences.

The information that was collected during the interview was treated as confidential and all participants' data was stored in a file with a unique participant identification number (e.g. MA001). All files were stored in a locked drawer in an office at the SU/UCT MRC and electronic data was stored on a password-protected computer.

All participants that presented with psychiatric comorbidity or who requested treatment for MA use were referred to an appropriate treatment provider. The interviewer provided a referral letter on request. After the interview, all participants received a R75 grocery voucher for time dedicated to the study.

Suggested Journal for Publication

This section proposes the suggested journal for publication of the research manuscript (Chapter 2). The "Instructions to Authors" can be seen in the Appendices as "Appendix 2".

For this research project the researcher (Edrich Rall), together with his supervisors (Prof Christine Lochner, SU; Dr Henk Temmingh, UCT), selected the Journal of Substance Use (Online; ISSN: 1475-9942) for publication of this manuscript. The Journal of Substance Use (Online) is an international peer-reviewed journal published in the United Kingdom by the Radcliffe Medical Press that aims to publish high-quality and original research and is accredited by the South African Department of Education.

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CHAPTER TWO

PUBLICATION-READY MANUSCRIPT

CLUSTER ANALYSIS OF DISORDERS CHARACTERISED BY IMPULSIVITY IN PATIENTS WITH METHAMPHETAMINE USE DISORDER

ABSTRACT

Background

Individuals with methamphetamine use disorder (MUD) frequently present with psychiatric comorbidities with impulsive features. Little research has been conducted on comorbidity with impulsive features in MUD. Therefore, this cross-sectional study aimed to delineate comorbid disorders with impulsivity in adult patients with a primary diagnosis of MUD.

Methods

Participants with lifetime MUD were included. Well established measures screened for comorbid psychiatric disorders with impulsive features. Illness severity was measured by the Yale Brown Obsessive-Compulsive Scale – adapted for drug use. The UPPS-P Impulsive Behavior Scale was used to assess impulsivity levels. A cluster analysis (CA) of lifetime comorbid disorders with impulsive features was performed. Demographic and clinical correlates of each identified cluster were identified.

Results

Sixty five (n = 65) adults with a primary diagnosis of MUD took part in the study. They were predominantly female (44 females; 21 males), with ages ranging between 18 and 44 years (mean = 30 years; SD = 6.53). The CA rendered 4 groups. Cases (n=12) in the “alcohol cluster” presented with AUD as their only *impulsive* disorder other than MUD. Cases (n=19) in the “healthy cluster” had no comorbidity. Cases (n=15) in the “antisocial cluster” all had comorbid antisocial personality disorder as well as polysubstance use disorders. Cases (n=19) in the “borderline cluster” had borderline personality disorder and polysubstance use disorders. Illness severity (Y-BOCS-du: p=0.03) and impulsivity levels (UPPS-P: p=0.01) differed significantly between the clusters. The “alcohol cluster” had the highest illness severity and the “antisocial cluster reported the highest levels of impulsivity.

Conclusion

The findings of this contribute to the paucity data on impulsivity in MUD and may have implications for treatment. Understanding how these conditions cluster in MUD, and remaining cognizant of the demographic and clinical correlates of each cluster in MUD, could potentially enable clinicians to identify patients who are at higher risk for engaging in risky behaviors rendering them more vulnerable to treatment non-adherence or relapse.

Keywords: Cluster analysis; Comorbidity; Impulsive comorbidity; Impulsivity; Methamphetamine use disorder; Substance use disorder

Introduction

Methamphetamine (MA) is a highly addictive stimulant and MA use has become is a major problem across the globe and especially so in the Western Cape Province of South Africa in recent years (Akindipe et al., 2014; Dada, Burnhams, et al., 2017). Methamphetamine use disorder (MUD) is characterized by a pattern of MA use that results in functional impairment (APA, 2013), with significant psychiatric comorbidity (e.g. (Akindipe et al., 2014; Harker et al., 2008; Kalechstein et al., 2000; Lin et al., 2004; Salo et al., 2011) ranging from anxiety (Akindipe et al., 2014; Salo et al., 2011) and mood disorders (Kalechstein et al., 2000; Plüddemann et al., 2013; Yen & Chong, 2006) to neurological problems, such as attention deficit hyperactivity disorder (ADHD) (Obermeit et al., 2013).

Methamphetamine use disorder has also been associated with problems with impulsivity (Brooks et al., 2017). Although not a psychiatric diagnosis in itself, impulsivity is a key feature of many psychiatric conditions (APA, 2013; Moeller et al., 2001). Impulsivity is frequently seen in personality disorders, such as antisocial- (ASPD) and borderline personality disorder (BPD) (Few, Lynam, & Miller, 2015; Kisa, Yildirim, & Göka, 2005; Robbins et al., 2012), and is a hallmark feature of the disruptive-, impulse control- and conduct disorders, and is also common in eating disorders, obsessive-compulsive and related disorders, and in SUDs (APA, 2013).

There is a paucity of research on MUD and comorbidity characterised by impulsivity. It has however been established that MA users have higher impulsivity as compared to healthy controls (Hoffman et al., 2006; Mahoney et al., 2015). Several studies have reported that disorders with impulsive features, such as ASPD, BPD, and other SUDs often co-occur with MUD (e.g. (Plüddemann et al., 2013; Salo et al., 2011). A better understanding of the relationship between impulsivity and other characteristics of MA users may have important clinical significance. It is with this in mind that this study aimed to delineate psychiatric comorbidity with impulsive features in adult patients with a primary diagnosis of MUD.

Firstly, structured diagnostic interviews were used to determine impulsive psychiatric comorbidity in individuals with MUD. It was hypothesized that the sample would have high rates of psychiatric comorbidity and more specifically, that disorders characterised with impulsivity would be common among individuals with MUD. Secondly, impulsive comorbid disorders in MUD were delineated using a CA method and it was hypothesized that comorbid disorders characterized by impulsivity will fall into 2 or more clusters. Thirdly, the associations of the identified clusters with

demographic (age, gender and level of education) and clinical variables (i.e. illness severity) were assessed using one-way analysis of variance (ANOVA).

Methods

This project was a secondary analysis of data collected by the Stellenbosch University (SU) / University of Cape Town (UCT) Medical Research Council's Unit on Risk and Resilience in Mental Disorders (SU/UCT MRC). The data analyzed was sourced from an ongoing project at this Unit, named "Gambling Disorder and MUD: A neurocognitive, genetic and neuroimaging study". This project was launched in September 2015 and received ethical approval from the IRBs of SU (reference number N14/05/053) and UCT (reference number 770/2014), respectively.

Adult males and females were recruited from the community through newspaper advertisements and from local treatment centers (inpatient and outpatient). Only individuals with a history of or current MA use were recruited for this study. Participants from treatment centers or other institutions were screened by a referral practitioner before referral to our study. If all of the inclusion criteria were met, participants were scheduled for a semi-structured interview. Inclusion criteria were: a primary diagnosis of MUD, aged between 18 and 65 years, and residing in the Western Cape Province of South Africa. Individuals with a history of other mental illnesses or abuse of additional (i.e. non-MA) substances were allowed to participate in the study. Individuals with a history of psychosis were excluded.

The majority of participants were interviewed at the SU/UCT MRC. Participants from inpatient treatment centers were seen at the respective facility and outpatient participants were either seen in an office at their treatment center or at the above-mentioned unit. After the interview at the SU/UCT MRC (done by the incumbent under supervision of Prof Christine Lochner, a registered clinical psychologist and principle investigator (PI) (of the parent project) the data was entered and organized in an electronic database. Data collection ended on 30 March 2018.

Assistance with statistical analysis was obtained from a statistician from the Centre of Statistical Consultation at the Department of Statistics and Actuarial Sciences at SU. A cluster analysis (Ward's method) (CA) was used to identify homogeneous groups within the MUD dataset (Statistics Solutions, 2018). A CA is an explanatory analysis that is used to identify structures in a dataset (Statistics Solutions, 2018). In theory, CA divides cases that are similar (high within group-

homogeneity) into groups, referred to as clusters (Clatworthy et al., 2005). Here, group entities (cases) were clustered on the basis of their similarities (comorbid diagnoses). This method is commonly used in psychiatry (Clatworthy et al., 2005) and deemed suitable to use with comorbidity (binary / categorical) data. "Ward's method" is a specific hierarchical clustering strategy that was used here to delineate disorders characterized by impulsivity in a sample of patients with a primary diagnosis of MUD.

A CA can perform a number of useful functions to organise large quantities of data (Clatworthy et al., 2005). Moreover, cluster analysis has the potential to make a major contribution to applied health psychology research through the identification of groups that might best benefit from interventions or further research (Clatworthy et al., 2005). Identifying these high-risk groups may ultimately guide the development of interventions for appropriate targets (Clatworthy et al., 2005).

Materials

Screening of potential participants was done telephonically or via email with a screening questionnaire (Appendix 3) and all participants provided signed consent for participation. The current version of the consent form can be seen in the appendices as "Appendix 4". After consent was provided, the interview commenced. A questionnaire with questions on demographics (i.e. age, sex, population (ethnicity), language, level of education, and occupation) was completed during the interview.

The Substance Use Disorder module of the Structured Clinical Interview for DSM-5 Disorders (SCID-5) was administered to diagnose MUD and other substance use disorders (sedatives, cannabis, stimulants, opioids, inhalants, phencyclidine, hallucinogens, and other).

The Mini-international neuropsychiatric interview (MINI) (Sheehan et al., 1994) was used to assess diagnostic status of other comorbidities (Lejoyeux et al., 2002). It assessed for depressive disorders (dysthymia, mania, and suicidality), anxiety disorders (panic disorder, agoraphobia, social anxiety disorder, general anxiety disorder, obsessive-compulsive disorder, and posttraumatic stress disorder), psychotic disorders and mood disorders with psychotic features, eating disorders (anorexia nervosa and bulimia nervosa), and ASPD.

The Structured Clinical Interview for the Diagnosis of Personality Disorders (SCID-II) was used to assess for borderline personality disorder (BPD) (Pihl, 2007). In addition to the SCID II, the

Structured Clinical Interview for the Diagnosis of Obsessive-Compulsive Spectrum Disorders (SCID-OCSD) (du Toit et al., 2001) was administered to assess impulse control disorders (ICD's), including kleptomania, pyromania, trichotillomania, and intermitted explosive disorder. The SCID-OCSD also assessed for "behavioral addictions", such as gambling disorder (GD).

The UPPS-P Impulsive Behavior Scale (UPPS-P) (Lynam, et al., 2006) was used to assess impulsivity. The UPPS-P is a 59-item self-report inventory, designed to measure personality pathways of impulsive behavior (Erfan, 2010). Participants responded to items on a four point Likert scale (1 - agree strongly, 2 - agree some, 3 – disagree some, 4 - disagree strongly) (Claes et al., 2015; Nathan Kline Institute, 2016), with higher scores suggesting increased rates of impulsivity. The UPPS-P also provides a total score that indicates the level of impulsivity of the respondent.

The Yale-Brown Obsessive-Compulsive Scale modified to reflect obsessions and compulsions related to drug use (Y-BOCS-du) (Friedman, Dar, & Shilony, 2000) was used to assess MA use severity. Items 1 to 5 comprise the obsessionality subscale and reflect drug-related thoughts whereas items 6 to 10 comprise the compulsivity subscale and reflect drug-related behaviors. The total score of the questionnaire is the sum of items 1 to 10 (range = 0 to 40). The internal consistency of the Y-BOCS-du has been reported to be 0.70 (Cronbach Alpha) (Friedman et al., 2000).
.A total of 16 disorders with impulsive features were included in the analysis, ranging from mood disorders, personality disorders, other SUDs, disruptive-, impulse control- and conduct disorders, and so called "behavioral addictions", to eating disorders, neurodevelopmental disorders, motor disorders, and obsessive-compulsive and related disorders (APA, 2013). Specifically, mood disorders such as bipolar disorder (BD) and some personality disorders, such as ASPD and BPD and other SUDs (other than MUD) were included. The SUDs were alcohol use disorder (AUD), other stimulant use disorders (e.g. cocaine), cannabis, and sedative hypnotics and anxiolytics (such as methaqualone / mandrax). Of the disruptive-, impulse-control-, and conduct disorders, intermitted explosive disorder (IED), pyromania, kleptomania, oppositional defiant disorder (ODD) compulsive shopping and GD were included. Impulsivity is furthermore regarded as an important feature in some eating disorders, resulting in the inclusion of bulimia nervosa and anorexia nervosa in the analysis. Of the neurodevelopmental disorders attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD) were included; and the obsessive-compulsive and related disorders included here

were obsessive-compulsive disorder (OCD) and trichotillomania (hair-pulling disorder). The accepted level of significance (alpha level and *p*-value) was < 0.05 for the appropriate statistical tests.

Results

Sixty five (n = 65) adults with a primary diagnosis of MUD took part in the study. They were predominantly female (44 females; 21 males), with ages ranging between 18 and 44 years (mean = 30 years; SD = 6.53). The majority of participants were of mixed race ancestry (n = 60; 92%), and unemployed (n = 47; 72%).

Of the 16 psychiatric disorders characterised by impulsivity that were investigated here, nine (9) featured in our sample. These ranged from personality disorders, SUDs (other than MUD), eating disorders, and disruptive, impulse control- and conduct disorders, neurodevelopmental disorders and obsessive-compulsive and related disorders.

Lifetime Impulsive Comorbidity

The lifetime prevalence of comorbidities with impulsivity was firstly determined. We found that 70% (n = 46) of cases with MUD met a lifetime diagnosis of any comorbid disorder characterised by impulsivity. More than a third (n = 23; 35%) of the cohort was diagnosed with a personality disorder; i.e. ASPD (n = 14; 21%) or borderline personality disorder (BPD) (n = 9; 13%). Substance use disorders were also high in this sample. Almost two-thirds of cases (n = 41; 63%) met a comorbid diagnosis of at least one SUD, other than MUD. Three comorbid SUDs were identified – alcohol use disorder (AUD), cannabis use disorder (CUD), and methaqualone / mandrax use disorder (MxUD). Of these, AUD was diagnosed in nearly half (n = 31; 47%) of the participants. Cannabis use disorder was diagnosed in almost a third of cases (n = 21; 32%) and MxUD in 24 (36%) of the participants.

Two participants had an eating disorder, i.e. anorexia nervosa and binge eating disorder, respectively. Of the disruptive, impulse control- and conduct disorders, 5 (7%) participants had a positive diagnosis; one participant was diagnosed with comorbid intermitted explosive disorder (IED) and another with kleptomania. Furthermore, three participants had a comorbid diagnosis of gambling disorder (GD) and four (6%) participants were diagnosed with attention deficit hyperactivity disorder (ADHD) and one with trichotillomania (hair-pulling disorder).

Cluster Analysis

The 65 cases were included in the CA. Using Ward's CA method with Euclidean distances heuristically, cases were clustered in 4 groupings at a linkage distance of 6.63, as depicted in a dendrogram (tree-diagram) (Figure 1). These comorbid disorders were ASPD, BPD, AUD, CUD and MxUD and were the only disorders identified at the given linkage distance (Figure 2).

In terms of impulsive comorbidity, Cluster 1 (n = 12), labeled the "alcohol cluster", had comorbid AUD only. Referred to as the "healthy cluster", cluster 2 cases (n = 19) reported no impulsive conditions other than MUD. Cluster 3 (n = 15), the "antisocial cluster" were diagnosed with ASPD and polysubstance use disorders, and Cluster 4 (n = 19), the "borderline cluster", had BPD and polysubstance use disorders, in addition to their primary MUD.

Associated Features of the Identified Clusters

Clusters did not differ from one another in terms of their demographic characteristics but notably, Cluster 1 cases ("alcohol cluster") were all female and cases in Cluster 3 ("antisocial cluster") were mostly male (60%). Eighty percent of the Cluster 3 cases had ASPD, 6% BPD, 46% AUD, 26% CUD, and 80% had MxUD. Ten percent of the cases in the "borderline cluster" (Cluster 4) had ASPD, 42% had BPD, 63% had AUD, 89% CUD, and 63% of MxUD.

There was a statistically significant difference in impulsivity level, as measured with the UPPS-P, between the clusters ($F(3, 61) = 3.54$; $m = 146.01$; $sd = 24.23$; $p = 0.01$) (Figure 3). Impulsivity in the "healthy cluster" was not significantly different from the "alcohol cluster", but was significantly lower than that of the "antisocial cluster" ($p = 0.01$) and "borderline cluster" ($p = 0.04$). Post hoc LSD-tests revealed that the "antisocial cluster" scored the highest in impulsivity, being significantly higher than the "alcohol cluster" and the "healthy cluster", but not in relation to the "borderline cluster". The "borderline cluster" reported the second highest in impulsivity, only being significantly different in this regard to the "healthy cluster".

Table 1: Total UPPS-P scores of each cluster.

UPPS-P	Cluster	UPPS-P total score	
		Mean	Standard deviation
	"Alcohol cluster"	136.00	24.23
	"Healthy cluster"	136.94	24.10
	"Antisocial cluster"	157.93	17.85
	"Borderline cluster"	152.00	23.93

For the Y-BOCS-du significant differences were reported between the clusters ($F(3, 61) = 2.97$; $m = 23.89$; $sd = 10.40$; $p = 0.03$) (Figure 4). Post hoc LSD-test comparisons on the Y-BOCS-du determined that cluster 1 ($p=0.01$) and 4 ($p=0.01$) were significantly more severely ill compared to cluster 2, and no differences in illness severity were reported between cluster 3 and the other clusters.

Table 2: Differences in illness severity between clusters as measured with the Y-BOCS-du.

Measure	Cluster	Total score (mean)	Std. deviation	p-value
Y-BOCS-du	Cluster 1: Alcohol cluster	27.50	8.78	0.03
	Cluster 2: Healthy cluster	18.68	9.82	
	Cluster 3: Antisocial cluster	23.40	11.30	
	Cluster 4: Borderline cluster	27.21	9.62	

Discussion

There has been little systematic investigation of the nature and implications of comorbidity of disorders characterized by impulsive features in MUD. Understanding how such conditions cluster in MUD, with their associated demographic and clinical features, may potentially guide selection of treatment targets, selecting appropriate interventions, harm reduction, and prevent relapse in MUD.

The main findings of this investigation were 1) that disorders characterised by impulsivity were common among individuals with MUD; 2) that impulsive comorbid disorders in MUD clustered into 4 clusters, which were subsequently labeled as the ”alcohol cluster”, “healthy cluster”, “antisocial”- and “borderline cluster”; and 3) that the antisocial MUD cluster was mostly male and had the highest impulsivity scores, and the ”alcohol cluster” was mostly female and had the highest illness severity scores, in comparison to the other clusters.

This study showed that psychiatric comorbidity was common in this population (e.g. Akindipe et al., 2014; Dada, Burnhams, et al., 2017; Harker et al., 2008; Morisano et al., 2014; Plüddemann et al., 2013). More specifically, 70% of our sample had a lifetime diagnosis of a psychiatric disorder with impulsive features. This was higher compared to reports from other local and international work on MUD and psychiatric comorbidity (such as Akindipe et al., 2014; Glasner-Edwards et al., 2010) and might be attributed to recruitment of most of the study sample from an inpatient psychiatric institution where they were following a rehabilitation program to address MUD and related problems.

As noted earlier, impulsivity and substance use often constitute elements of a vicious cycle; i.e. impulsivity may increase the likelihood of using stimulants such as methamphetamine, which in turn may increase impulsivity, again leading to potentially hazardous drug use and other risky behaviors. It thus makes sense that comorbid psychiatric disorders characterized by impulsivity in MUD may increase the risk of abusing other substances (Conway, Compton, Stinson, & Grant, 2006) and it has been suggested that the most prevalent comorbidities in psychiatric populations (Weich & Pienaar, 2009) and in MUD (Salo et al., 2011) are other SUD’s. The CA conducted here identified four clusters: an “alcohol cluster”, a “healthy cluster”, an “antisocial cluster”, and a “borderline cluster”. Cases in all clusters, except the “healthy cluster” abused one or more substances other than MA. In particular, cases in clusters 3 and 4 were also marked with polysubstance (in addition to MA) use disorders.

In terms of demographic correlates, it is notable that the “alcohol cluster” comprised of females only. It has been suggested that women may be less likely to abuse illicit substances (Dove & Joseph, 2007; Hecksher & Hesse, 2009), but are more likely to have problems with alcohol (Dove & Joseph, 2007; Vythilingum, Roos, Faure, Geerts, & Stein, 2012). Alcohol abuse may however have rendered this group more vulnerable to MA use. This group also presented with highest illness severity scores, suggesting that the combination of MA use, alcohol use disorder and female gender

present a particularly vulnerable group. This was partly consistent with other work suggesting that women with alcohol-related problems had increased illness severity (McCutcheon et al., 2011). The predominance of males in the antisocial MUD cluster is consistent with other work suggesting a strong link between ASPD and male gender (Chun et al., 2017). Cases in this cluster presented with a combination of ASPD, male gender and MUD, and had the highest impulsivity scores compared to the others, suggesting that this is a particularly high risk group of individuals. The antisocial MUD cluster cases had increased rates of ASPD and polysubstance use disorders. Individuals with ASPD often present with an increased number of SUDs (Ogloff, Talevski, Lemphers, Wood, & Simmons, 2015). Similar, the current study found that MUD with comorbid ASPD was associated with co-occurring SUDs, as 80% of cases this cluster met the diagnosis of MxUD, 46% AUD, and 26% CUD.

The associated features of the "borderline cluster" were expected: these cases were predominantly female (63%) and reported the highest rates of polysubstance use disorders in comparison to the other clusters. The link between BPD and female gender has been repeatedly reported (Chun et al., 2017). In addition, BPD has also often been linked to polysubstance use (Trull, Sher, Minks-Brown, Durbin, and Burr, 2000). The majority of cases in the current study (89%) met a comorbid diagnosis CUD and had high rates of AUD (63%) and CUD (63%).

The correlation of the two clusters characterised by personality disorders (i.e. the antisocial- and borderline clusters) with polysubstance use disorders are consistent with existing literature that have suggested a link between personality pathology and substance abuse. This might be attributed to common underlying features, such as personality characteristics such as impulsivity (Dellazizzo et al., 2018), genetic, behavioural and cognitive factors (Rzhetsky, Wajngurt, Park, & Zheng, 2007; Smith, Mattick, Jamadar, & Iredale, 2014), or shared risk markers for externalizing behaviors of these conditions (Brook, Zhang, Rubenstone, Primack, & Brook, 2016; Trull et al., 2000).

Impulsivity has frequently been associated with SUDs (Taylor et al., 2016) and studies have suggested high levels of impulsivity in these populations (e.g. Hoffman et al., 2006; Mahoney et al., 2015; Moeller et al., 2001). Increased substance use comorbidity was associated with higher levels of impulsivity (Smith et al., 2014) and the findings here indicated that additional impulsive comorbidity was also linked with greater impulsivity in general. Smith et al. (2014) indicated that having a smaller number of SUDs were linked to lower impulsivity levels. This finds support in our finding that cases in

the “alcohol”- and “healthy” clusters scored lower on the UPPS-P in comparison to the “antisocial”- and “borderline” cluster.

The results may potentially guide understanding of the ways in which MUD present, of the risk factors to consider during care, and may ultimately assist in improving outcomes in these patients. Cognizance of the demographic and clinical correlates of impulsivity in MUD may aid practitioners in providing appropriate treatment to selected targets. For example, it may be suggested that MUD cases that fit the cluster 3 profile (i.e. male, with comorbid ASPD and polysubstance use) may benefit from treatments that include impulse and aggression control components. Similarly, illness severity of patients that fit the profile of the borderline MUD cluster (likely female, with comorbid BPD) would likely be very high, potentially necessitating additional support on multiple levels, including assistance with personality- or interpersonal difficulties.

There are a few study limitations deserving mention. First, the sample was mostly female which is atypical as most other MUD studies suggest an association between MUD and male gender (Akindipe et al., 2014). The female preponderance of the current investigation resulted from the initial recruitment drives at clinics with female patients only. However, this makes the finding of a connection between the antisocial MUD cluster and male gender even more noticeable. Second, most of the sample was recruited from drug treatment centers, psychiatric institutions, and other health care practitioners, which may limit the extent of generalisability of our findings to the population of MA dependent individuals within the community. Thirdly, the small sample size may also be a limitation. Finally, this project was limited by the overarching project’s data which did not include all conditions with impulsive features (e.g. histrionic personality disorder and narcissistic personality disorder were not assessed and the data thus not available).Future studies on impulsive comorbidity in patients with MUD may benefit from a more gender-balanced and a larger sample, recruited from several different contexts (clinic and community). Inclusion of all conditions characterized by impulsivity should be emphasized to provide a comprehensive overview of impulsive comorbidity in MUD.

Conclusion

In conclusion, MA use has increased globally in recent years, reaching epidemic proportions in South Africa, particularly in the Western Cape Province. This study responded to pleas that highlighted the need for further research on MA use locally - as a matter of social development, safety and public

health. The findings contribute to the paucity of research on MUD and comorbid disorders characterized by impulsivity. Understanding how these conditions cluster in MUD, and remaining cognizant of the demographic and clinical correlates of each cluster in MUD, could potentially enable clinicians to identify patients who are at higher risk for engaging in risky behaviors rendering them more vulnerable to treatment non-adherence or relapse. Such an understanding may potentially guide treatment strategies, and ultimately improve outcome in these patients.

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APPENDIX 1

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 404 7682
Email: nosi.tsame@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

12 March 2018

HREC REF: 074/2018

Prof D Stein
Psychiatry and Mental Health
Human Resources Development centre (aka Doctors bungalows)
Entrance and Maternity parking
2nd Floor, DB2
Groote Schuur Hospital

Dear Prof Stein

PROJECT TITLE: CLUSTER ANALYSIS OF COMORBID DISORDERS CHARACTERIZED BY IMPULSIVITY IN PATIENTS WITH METHAMPHETAMINE USE DISORDER (MPHIL CANDIDATE - MR E RALL) SUB-STUDY LINKED TO 770/2014

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 March 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student Mr E Rall will be involved in this study.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.

APPENDIX 2

Author Guidelines for the Journal of Substance Use

Extracted from: https://www.tandfonline.com/action/authorSubmission?journalCode=ijsu20&page=instructions

Instructions for authors

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Manuscripts should be in English and up to 3000 words in length. Articles of any length will be considered. Please discuss longer articles with the Editor before submission.

Structure

Your paper should be compiled in the following order: title page; abstract; keywords; main text introduction, materials and methods, results, discussion; acknowledgments; declaration of interest statement; references; appendices (as appropriate); table(s) with caption(s) (on individual pages); figures; figure captions (as a list).

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Papers may be submitted in any standard file format, including Word and LaTeX. Figures should be saved separately from the text. The main document should be double-spaced, with one-inch margins on all sides, and all pages should be numbered consecutively. Text should appear in 12-point Times New Roman or other common 12-point font.

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References

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Author details. All authors of a manuscript should include their full name and affiliation on the cover page of the manuscript. Where appropriate, please also include ORCiDsand social media handles (Facebook, Twitter or LinkedIn). One author will need to be identified as the corresponding author, with their email address normally displayed in the published article. Authors' affiliations are the affiliations where the research was conducted. If any of the named co-authors moves affiliation during the peer-review process, the new affiliation can be given as a footnote. Please note that authorship

may not be changed after acceptance. Also, no changes to affiliation can be made after your paper is accepted.

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Keywords. Keywords are the terms that are most important to the article and should be terms readers may use to search. Authors should provide 3 to 5 keywords. Please read our page about making your article more discoverable for recommendations on title choice and search engine optimization.

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Figures. Figures should be high quality (600 dpi for black & white art and 300 dpi for color). Figures should be saved as TIFF, PostScript or EPS files. Figures embedded in your text may not be able to be used in final production.

Tables. Please supply editable table files. We recommend including simple tables at the end of your manuscript, or submitting a separate file with tables.

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Please ensure that all research reported in submitted papers has been conducted in an ethical and responsible manner, and is in full compliance with all relevant codes of experimentation and legislation. All papers which report *in vivo* experiments or clinical trials on humans or animals must include a written statement in the Methods section. This should explain that all work was conducted with the formal approval of the local human subject or animal care committees (institutional and national), and that clinical trials have been registered as legislation requires. Authors who do not have formal ethics review committees should include a statement that their study follows the principles of the Declaration of Helsinki.

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promoting and increasing the visibility of your article. Here are some tips and ideas on how you can work with us to promote your research.

APPENDIX 3

Recruitment Screening Questionnaire

Date pt. called/emailed:_____

Date pt. was called back/emailed:_____

Recruited via:_____

Name & Surname:_____

Cell:_____

Work:_____

Home:_____

Email:_____

	MUD		
1	MA primary drug of use?	yes	no
2	History of other drug use	yes	no
3	History of psychopathology	yes	no

Notes: _____

_____

_____

_____

_____

_____

_____

_____

Suggested date of assessment:_____

Location of assessment:_____

Date of assessment confirmed by pt.?:_____

APPENDIX 4

Participant Consent Form

PARTICIPANT INFORMATION AND INFORMED CONSENT FORM

(PATIENTS)

TITLE OF RESEARCH PROJECT: Gambling disorder and methamphetamine use disorder: A neurocognitive, genetic and neuroimaging study

REFERENCE NUMBERS: **SU HREC:** N14/05/053

UCT HREC: 770/2014

PRINCIPAL INVESTIGATORS: **SU:** Prof Christine Lochner

UCT: Prof Dan Stein

ADDRESS: MRC Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry, Faculty of Medicine and Health Sciences, Stellenbosch University

CONTACT NUMBERS: Lochner: 021 – 938 9179; Stein: 021 – 404 2174

We would like to invite you to participate in a research study that involves genetic analysis and possible long-term storage of blood or tissue specimens. Please take some time to read the information presented here which will explain the details of this project. Please ask the study staff any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is **entirely voluntary** and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part initially.

This research study has been approved by the **Health Research Ethics Committee at Stellenbosch University and the Human Research Ethics Committee at the University of Cape Town** and it will be conducted according to international and locally accepted ethical guidelines for research, namely

the Declaration of Helsinki, and the SA Department of Health's 2004 Guidelines: *Ethics in Health Research: Principles, Structures and Processes.*

What is genetic research?

Genetic material, also called DNA, is usually obtained from a small blood sample. Occasionally genetic material is obtained from other sources such as saliva. Genes are found in every cell in the human body. Our genes determine what we look like and sometimes our susceptibility to certain kinds of diseases. Worldwide, researchers in the field of genetics are continuously discovering new information. This information may be of great benefit to both future generations and people today, who suffer from particular diseases or conditions.

What does this particular research study involve?

This study is part of a research project we are conducting to learn more about gambling disorder and methamphetamine use disorder.

Doctors and scientists at the MRC Unit on Risk and Resilience in Mental Disorders, University of Stellenbosch, and the Department of Psychiatry, University of Cape Town, are collaborating with researchers from other research institutions worldwide to investigate the structure and functioning of selected brain areas in 40 individuals with gambling disorder and 40 individuals with methamphetamine use disorder. This study also aims to identify the genes that may increase the risk for the development of these conditions. Information from patients will be compared with 40 age- and gender-matched healthy controls.

This is not a treatment study. Information is being collected for research purposes only.

Why have you been invited to participate?

You have been invited to participate because you have indicated (either to your doctor, or to the National Responsible Gambling Programme's telephone counselling line which is affiliated with UCT's Addiction division) that you excessively gamble or use methamphetamine ("tik") to the extent that it affects your functioning.

Gambling disorder (GD) or pathological gambling can be defined as the inability to resist the urge to gamble despite severely negative personal or social consequences. Similarly, methamphetamine use disorder (MUD) refers to the inability to resist taking the drug, and is often associated with repeated unsuccessful attempts to cut down, resulting in a failure to fulfill major obligations at work, school or home.

What procedures will be involved in this research?

If you decide to participate, we will ask you to attend 2-4 sessions, each with a different study focus.

The first session will comprise an interview with a researcher and the drawing of bloods. These procedures will last approximately 3-4 hours (with a break in-between, if need be). Depending on the preferences of your treatment centre, this session may be broken up into two sessions and the drawing of bloods and completion of questionnaires may be conducted in a group setting. The clinical interview will, amongst other things, include a number of questions related to gambling or methamphetamine use and your prior psychiatric history. Approximately 20 ml (4 teaspoons) of blood will be drawn from your arm. We may need to contact you again to get another blood sample should we fail to get a DNA sample (the genetic material) from your blood. The blood sample you give may be used to create a cell line. A cell line is living tissue that can be used to make more of your DNA at any time in the future. Genetic material previously found to be associated with gambling disorder which may also play a role in brain activity, will also be investigated. This process will take place at the Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, at the University of Stellenbosch. Should you not wish to provide us with a blood sample, you may provide us with a saliva sample instead.

The second session will involve 2 hours of brain scanning followed by neuropsychological testing (i.e. computer based tasks to test abilities such as decision making) of approximately 1.5 hours' duration. This session may also be broken up into two sessions, depending on your or your treatment centre's preference, as well as transport availability. MRI (brain scanning) makes use of magnetic fields and radio waves to examine internal structures of the body. The procedure is non-invasive and completely

harmless. No ionising radiation (such as X-rays) or radio-active material are used during the study. MRI is particularly useful for imaging soft tissue such as the brain. It is capable of measuring certain characteristics of brain function. The procedure requires that you lie on your back with your head in a "tunnel" which is very similar to a CAT scan machine. The tunnel is open on both sides and is well lit and ventilated. You will at all times be in intercom contact with the radiographer, who will also be able to see you at all times. The examination will take about 90 minutes (with breaks if needed) and will be accompanied by a series of loud knocking sounds. There are no moving parts within the scanner, and the knocking sounds occur due to vibration of the machine in the magnetic fields. In some instances, the intravenous administration of contrast agent is also necessary, but you will be notified in advance about this. Finally, it is important that you do not move at any stage during the examination as this makes the images blurry.

The initial screening and assessment of GD or MUD patients as well as the drawing of bloods will take place either at the National Responsible Gambling Programme (NRGP) offices in Kenilworth, at the Faculty of Medicine and Health Sciences at the Tygerberg Campus of Stellenbosch University, or at the rehabilitation centre where you are currently being treated, depending on your preference for either location. The brain imaging will proceed at the recently established scanning centre at Groote Schuur Hospital (UCT). The computer-based tasks will proceed at the Faculty of Medicine and Health Sciences at the Tygerberg Campus of Stellenbosch University. You will receive grocery vouchers for participation and refreshments will be provided if requested. Where necessary, transport will also be provided.

We may contact you later for further information, or request you to complete another interview at a later date, in order to obtain follow-up information that may be of use in our genetic analyses. This may involve an assessment similar to the current assessment, including a series of interviews and/or another blood sample. Your current participation is in no way binding to your future participation.

Are there any risks involved in participation?

There are no more than minimal medical or psychological risks associated with this study. If you feel fatigued, uncomfortable, or in any way upset during any part of the session(s), you may ask to stop for

a rest break or have the interview or scanning discontinued. The research interview does not take the place of a full psychiatric evaluation. You may experience some emotional discomfort when answering some questions. If any particular question makes you feel uncomfortable, you may discuss its importance with the specially trained interviewer. You may choose not to answer any question should you feel uncomfortable.

You may feel some pain associated with having blood drawn from a vein. You may experience discomfort, bruising and/or other bleeding at the site where the needle is inserted. Occasionally, some people experience fleeting dizziness or feel faint when their blood is drawn. Some insurance companies may mistakenly assume that your participation in this study is an indication that you are at higher risk of a genetic disease, and this could hurt your access to health or other insurance. We will not share any information about you, or your family, with an insurance company. It is the opinion of the investigators that participation in this study does not constitute genetic testing. Therefore, participation in this study should not be reported as genetic testing.

You may feel some discomfort or fatigue associated with being in the brain scanner or while undergoing neuropsychological testing.

Are there any benefits to your taking part in this study? Will the results of your participation be discussed with you?

This study will hopefully provide useful data about the nature of problem gambling in South Africa, potentially filling gaps in the current body of knowledge regarding gambling. Individuals who might develop one of these conditions in the future, their family members, and future generations may benefit from the project if we can locate the genes and brain structures or functions that may have led to these symptoms. That knowledge may then be used for prevention or treatment planning and policy purposes

Individuals who choose not to partake in this study are free to do so at no consequence and will be referred for treatment, if requested.

How long will your blood/DNA sample be stored and where will it be stored?

Samples will be safely stored at -80 degrees Celsius at the Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, at the University of Stellenbosch, and de-identified (identified by a code number), and access will be limited to authorised scientific investigators. We also collaborate with researchers abroad; this means we may in future share DNA samples and anonymous (clinical or imaging) information with these sites to study your condition.

Your DNA will be maintained permanently, unless you request to have it removed. If at any time in the future you wish to have your DNA or clinical data removed from the storage site, you may do so by contacting the researchers conducting this study.

Will your clinical and genetics information be used for other research?

You can choose to share your clinical and DNA information with other scientists through a central database. In other words, the data that have been collected may be used for future investigations. Other researchers would be able to learn from your data and would be able to conduct studies that include DNA from many countries. This can lead to larger and better studies related to gambling disorder, methamphetamine use disorder and other health conditions.

An “online database” is a database that is created from the central database. Researchers all over the world have access to this database (this is called “data sharing”). The DNA stored in this online database will be used for research into general medical conditions OR psychiatric illnesses. If South African researchers wish to use your stored blood/DNA for additional research in this field, they will be required to apply for permission to do so from the Health Research Ethics Committee at Stellenbosch University and the Human Research Ethics Committee at the University of Cape Town. If researchers from abroad wish to use your DNA information that has been stored on the online database, they will be required to apply for permission to do so from the National Institute of Health in the United States of America. If you wish to withdraw your data or your sample in the future, this is possible. However, please note that by the time we withdraw your data or your sample, it may already have been shared with other researchers. The United States National Institute for Mental Health (NIMH) Repository would, however, then instruct researchers to destroy your data and your sample if requested.

Will your brain imaging data be shared with other researchers?

In the same way as above, you can also choose to share your brain imaging data with researchers from other research institutions worldwide, to investigate, the structure and functioning of selected brain areas (anonymously).

How will your confidentiality be protected?

If you consent to participate in this study, your identity will be kept confidential. Your answers will not be shared with other family members or anyone else except for staff members involved in this study. All research information and laboratory samples obtained from you will be safely stored and identified by code number. This means that no identifying information will be shared. Access will be limited to authorised scientific investigators. Any publications resulting from this study will not identify you by name.

Because some of your DNA/cells are going to be stored in the United States, there is a very small chance the United States government might forcibly gain access to it using one of their laws called "The Patriot Act". This Act is used when the United States government judges that access to DNA is important for security purposes.

Will you or the researchers benefit financially from this research?

You will not be paid to take part in this study although your travel expenses will be reimbursed. In addition to this, you will have the opportunity of winning some money in a monetary reward task. The exact amount you will receive is dependent on your performance on the task.

Is there anything else that you should know or do?

You can contact the principal investigator at Stellenbosch University, Christine Lochner, on 021 – 938 9179 or **CL2@sun.ac.za**, or the principal investigator at the University of Cape Town, Dan Stein, on 021 – 404 2164 or **dan.stein@uct.ac.za** , if you have any further queries or encounter any problems. You can contact the UCT Faculty of Health Sciences Human Research Ethics Committee at 021 –

406 6346 if you have any concerns or complaints that have not been adequately addressed by study staff.

Declaration by participant

By signing below, I ……..……. agree to take part in a genetic research study entitled **Gambling disorder and methamphetamine use disorder: A neurocognitive, genetic and neuroimaging study**.

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is voluntary and I have not been pressurised to take part.
- I have received a signed duplicate copy of this consent form for my records.

Tick the options that apply:

☐ I agree to take part in the study and consent to my blood being drawn. My anonymized information and blood sample will be stored and used for the current research project. Please destroy my DNA sample as soon as the current research project has been completed.

☐ I agree that my anonymized information and blood or DNA sample can be stored**,** but I can choose to request at any time that my stored sample be destroyed. I have the right to receive confirmation that my request has been carried out.

☐ I agree that my anonymized information and blood or DNA sample can be made available on an online database for use by other researchers, but I can choose to request that my stored sample be destroyed. I have the right to receive confirmation that my request has been carried out.

☐ I agree that my anonymized brain imaging information can be made available for use by other researchers.

Signed at (*place*) ..... on (*date*) .....

....

Signature of participant **Signature of witness**

Declaration by investigator

I *(name)* …… declare that:

- I explained the information in this document to ……..……...
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research as discussed above.
- I did/did not use an interpreter. (*If an interpreter is used then the interpreter must sign the declaration below).*

Signed at (*place*) .....….....…….. on (*date*) ……...…….. .

....

Signature of investigator **Signature of witness**

Declaration by interpreter

I *(name)* …… declare that:

- I assisted the investigator (*name*) ……. to explain the information in this document to (*name of participant*) …….. using the language medium of Afrikaans/Xhosa.
- We encouraged him/her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Signed at (*place*) .....…..…….. on (*date*) ……...…….. .

....

Signature of interpreter **Signature of witness**

TABLES

Table 1: Differences in impulsivity between clusters as measured with the UPPS-P.

	Cluster	Mean	Standard deviation
UPPS-P	"Alcohol cluster"	136.00	24.23
	"Healthy cluster"	136.94	24.10
	"Antisocial cluster"	157.93	17.85
	"Borderline cluster"	152.00	23.93

Table 2: Differences in illness severity between clusters as measured with the Y-BOCS-du.

Measure	Cluster	Total score (mean)	Std. deviation	p-value
Y-BOCS-du	Cluster 1: Alcohol cluster	27.50	8.78	0.03
	Cluster 2: Healthy cluster	18.68	9.82	
	Cluster 3: Antisocial cluster	23.40	11.30	
	Cluster 4: Borderline cluster	27.21	9.62	

FIGURES

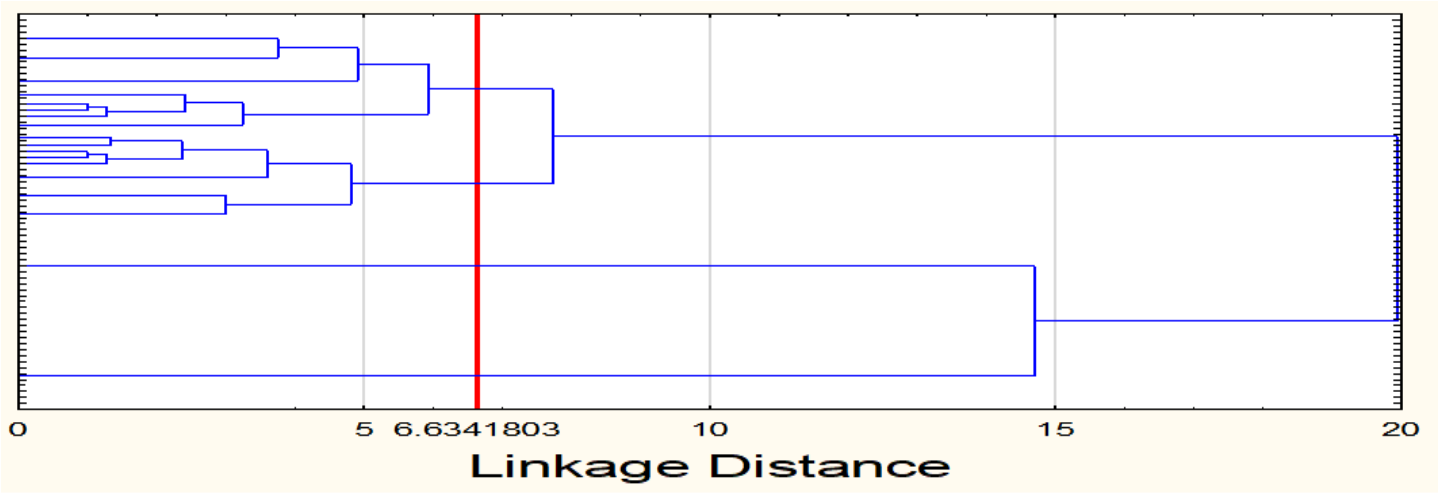

Figure 1: Dendrogram (tree-diagram) of 65 cases with Euclidean distances and a linkage distance of 6.63 that divides the sample into 4 clusters. The X-axes represents all cases included.

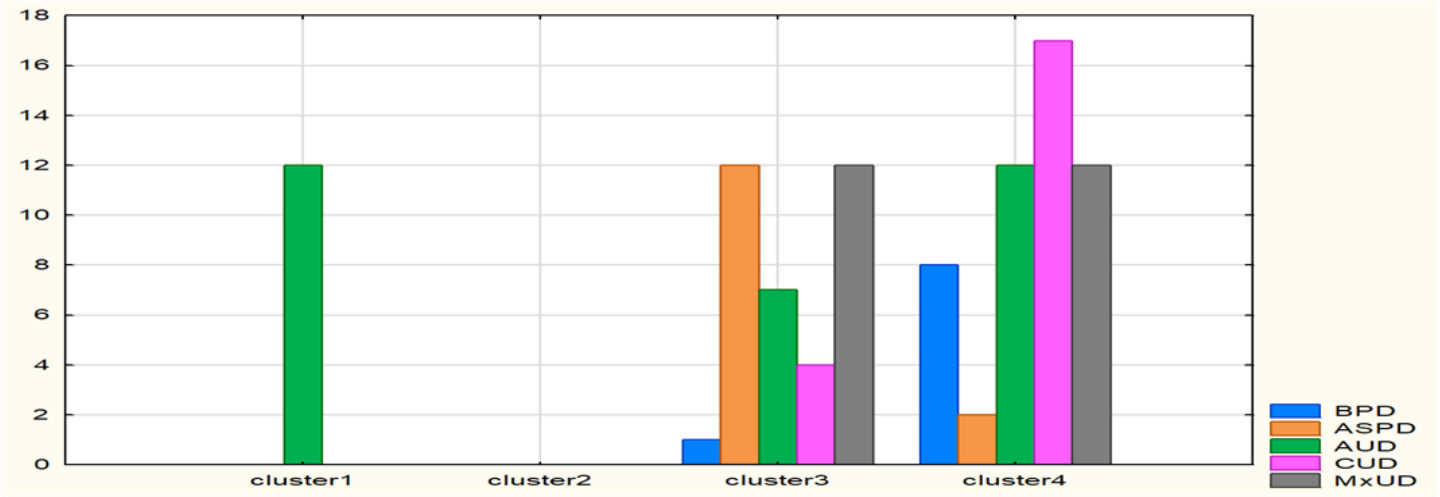

Figure 2: Cases clustered according to impulsive comorbidities.

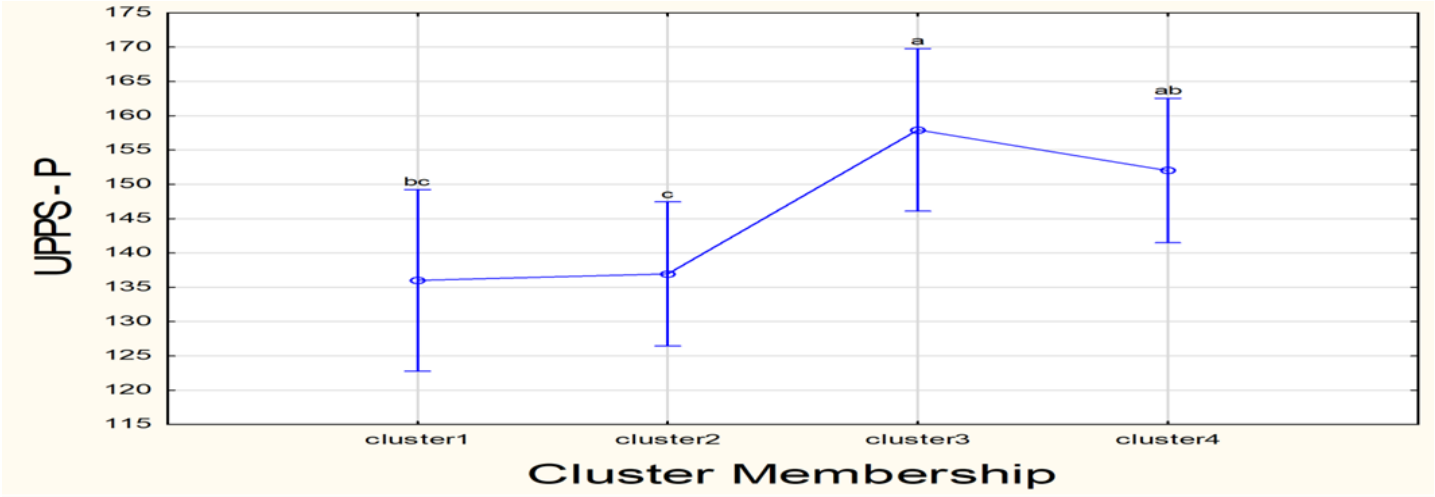

Figure 3: Differences in total impulsivity between clusters, as measured with the UPPS-P.

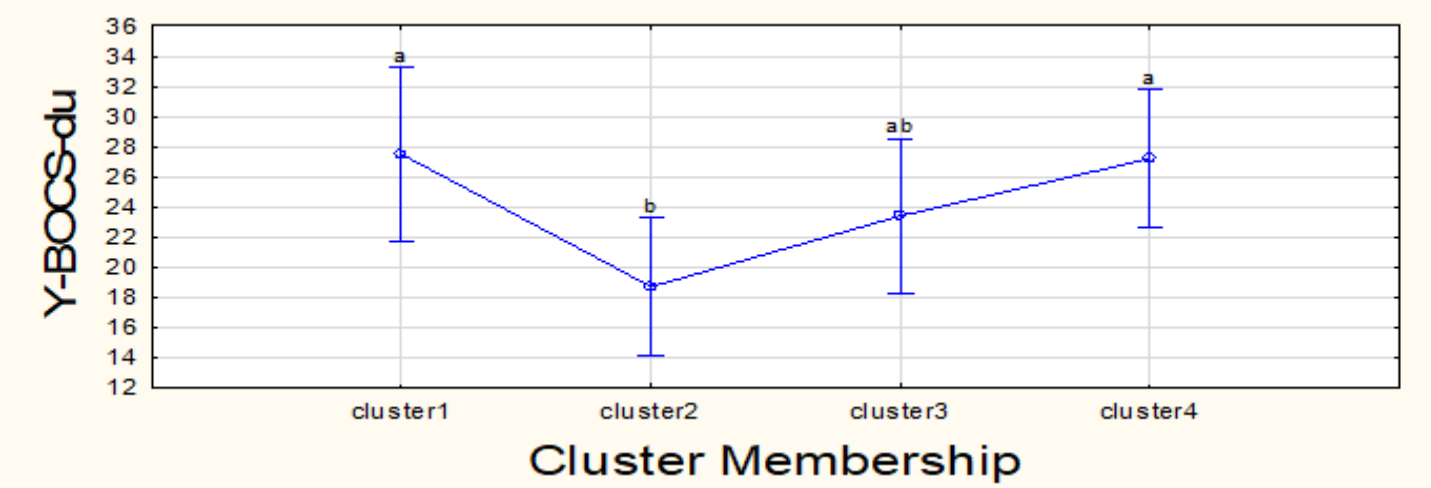

Figure 4: Illness severity between clusters as measured with the Y-BOCS-du

DECLARATION OF INTEREST STATEMENT

The authors report no conflict of interest